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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/321,655	05/28/1999	STANTON L. GERSON	CWR-7091NP	6848

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
06/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/321,655	GERSON, STANTON L.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/18/09 has been entered.

Amended claims 2-5 and new claim 6 are pending in the present application, and they are examined on the merits herein.

Sequence Non-Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth below.

This application contains **primer sequences on page 12 that have not been identified with particular SEQ ID NOs. in either a paper sequence listing and/or computer readable form (CRF) of the sequence listing**.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction

of the following is required: the phrase "***human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a to a medium which contains factors which stimulate mesenchymal cell growth without differentiation" recited in new claim 6.***

Claim Objections

Claim 6 is objected to because of the term "to a" is repeated twice in claim 6. Appropriate correction is required.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 recites the limitation "***human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a to a medium which contains factors which***

stimulate mesenchymal cell growth without differentiation'". In the amendment filed on 5/18/09, Applicants cited that the support for this new claim can be found in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 which are incorporated by reference on page 5, lines 2-5 of the present application. Upon examination of page 5, lines 2-5 of the as-filed specification, there is no indication and/or suggestion that any of the U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584 has been incorporated by reference.

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of invention as claimed at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995, Cited previously) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or (Mesenchymal stem cell-Wikipedia, the free encyclopedia, page 1-5, 2009). ***This is a modified rejection.***

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by 4th passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells (Abstract, and column 1, page 102). The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells (column 1, third paragraph, page 102), and it contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms “Mesenchymal stem cell” and “Marrow stromal cell” have been used interchangeably in the art as evidenced by Wikipedia, the free encyclopedia. Therefore, the bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue. With respect to new claim 6, the examiner interprets the limitation "human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation” is a product-by-process; and as such the isolated bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are

indistinguishable from these mesenchymal stem cells for the reasons already outlined above. Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Nolta et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Accordingly, the method taught by Nolta et al meets every limitation of the claims as written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 5/18/09 (pages 4-8 and 12-13) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that unlike the MSCs of the present application which lack surface markers for T and B lymphocytes, macrophages and endothelial cells and are prepared using detailed procedures described in U.S. Patent Nos. 5,197,985 and 5,226,914 and WO 92/22584, the heterogeneous adherent bone marrow stromal cells using the crude plastic adherence methods described by Nolta et al and Prockop are not equivalent to the isolated, purified and culturally expanded mesenchymals tem cell population even if the stromal cells are devoid of most hematopoietic cells and contains some MSCs. Applicants also argue that Nolta et al do not teach MSCs which have been further isolated, purified and culturally expanded from a mesodermic tissue. Applicants further argue that none of the cited references teach the new limitation in claim 6.

Firstly, please note that **the bone marrow stromal cell population** derived from bone marrow spicules **(after passage no. 4)** as taught by Nolta et al. **is devoid of most hematopoietic cells (column 1, third paragraph, page 102) and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop. Moreover, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art** as evidenced by Wikipedia, the free encyclopedia. **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells at the 4th passage for transfection, Nolta et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells**. The lack of most hematoietic

cells in the utilized 4th passaged bone marrow stromal cell population is also another evidence of purification.

Secondly, it is noted that **the claimed method does not contain specific steps by which human mesenchymal stem cells are isolated, purified or culturally expanded** such as those described in U.S. Patent Nos. 5,197,985 and 5,226,914 and WO 92/22584 as Applicants tried to distinguish a human mesenchymal stem cell population prepared by these specific methods from the bone marrow stromal cells or mesenchymal cells taught by Nolta et al and Prockop.

Thirdly, it is further noted that the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). This citation was used to demonstrate that a much less purified, much more heterologous Dexter stromal cells (passaged only once) was shown to be **at least functionally equivalent to hMSCs of the present invention**, let alone for the 4th passaged human allogeneic bone marrow stromal cells devoid of most hematopoietic cells used for transfection by Nolta et al.

Fourthly, with respect to new claim 6, the examiner interprets the limitation "human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a

medium which contains factors which stimulate mesenchymal cell growth without differentiation" is a product-by-process; and as such the isolated bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are indistinguishable from these mesenchymal stem cells for the reasons already outlined above. Please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claims 2 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al. (Gene therapy 2:512-520, 1995) as evidenced by Prockop, D.J. (Science 276:71-74; Cited previously) and/or (Mesenchymal stem cell-Wikipedia, the free encyclopedia, page 1-5, 2009). ***This is a modified rejection.***

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of an autologous bone marrow

stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5 (see at least Abstract and Materials and Methods, particularly pages 518-519). The utilized bone marrow stromal support contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms “Mesenchymal stem cell” and “Marrow stromal cell” have been used interchangeably in the art as evidenced by Wikipedia, the free encyclopedia. Therefore, the bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue. With respect to new claim 6, the examiner interprets the limitation "human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation” is a product-by-process; and as such the isolated bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells et al are indistinguishable from these mesenchymal stem cells for the reasons already outlined above. Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or

substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Accordingly, the method taught by Wells et al meets every limitation of the claims as written. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 5/18/09 (pages 8-13) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that unlike the MSCs of the present application which lack surface markers for T and B lymphocytes, macrophages and endothelial cells and are prepared using detailed procedures described in U.S. Patent Nos. 5,197,985 and 5,226,914 and WO 92/22584, the heterogeneous adherent bone marrow stromal cells using the crude plastic adherence methods described by Wells et al and Prockop are

not equivalent to the isolated, purified and culturally expanded mesenchymals tem cell population even if the stromal cells are devoid of most hematopoietic cells and contains some MSCs. Applicants also argue that Wells et al do not teach MSCs which have been further isolated, purified and culturally expanded from a mesodermic tissue. Applicant also argues that the Prockop reference states "The adherent cells used as feeder layers for HSCs have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of nonadherent cells, but it is not clear whether they retain the potential to differentiate into bone, cartilage, and other mesenchymal cells, or whether they have differentiated into another and discrete phenotype because of their continue interaction with hematopoietic cells" (page 72, col. 3, bottom first paragraph), and therefore the Prokop reference even suggests that the adherent cells may have differentiated into another and discrete phenotype because of their continuing interaction with hematopoietic cells. Lastly, Applicants argue that none of the cited references teach the new limitation in claim 6.

Firstly, please note that that the bone marrow stromal cell population obtained between passages 3 and 5 of Wells et al. **is depleted of hematopoietic cells and macrophages, and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop. Moreover, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art** as evidenced by Wikipedia, the free encyclopedia. **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells between passage 3 and passage 5 for transfection,**

Wells et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells. The depletion of hematoietic cells and macorphages in the utilized 4th passaged bone marrow stromal cell population is also another evidence of purification.

Secondly, it is noted that **the claimed method does not contain specific steps by which human mesenchymal stem cells are isolated, purified or culturally expanded** such as those described in U.S. Patent Nos. 5,197,985 and 5,226,914 and WO 92/22584 as Applicants tried to distinguish a human mesenchymal stem cell population prepared by these specific methods from the bone marrow stromal cells or mesenchymal cells taught by Wells et al and Prockop.

Thirdly, with respect to the cited passage concerning whether adherent feeder layer cells retain the potential to differentiate into bone, cartilage, and other mesenchymal cells, or whether they have differentiated into another and discrete phenotype because of their continue interaction with hematopoietic cells; once again please note that the bone marrow stromal cell population obtained between passages 3 and 5 of Wells et al is depleted of hematopoietic cells for any interaction. Furthermore, there is no factual evidence indicating that despite **having many of the characteristics of MSCs isolated by their adherence to plastic in the absence of nonadherent cells**, adherent feeder layer cells would not retain the potential to differentiate into bone, cartilage, and other mesenchymal cells.

Fourthly, it is further noted that the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34

human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). This citation was used to demonstrate that a much less purified, much more heterologous Dexter stromal cells (passaged only once) was shown to be **at least functionally equivalent to hMSCs of the present invention**, let alone for the 4th passaged human autologous bone marrow stromal cells devoid of most hematopoietic cells and macrophages used for transfection by Wells et al.

Fifthly, with respect to new claim 6, the examiner interprets the limitation "human mesenchymal stem cells that have been isolated, purified and culturally expanded from a bone marrow specimen by adding the bone marrow specimen to a medium which contains factors which stimulate mesenchymal cell growth without differentiation" is a product-by-process; and as such the isolated bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are indistinguishable from these mesenchymal stem cells for the reasons already outlined above. Please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness"

under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633